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09/847,102	05/01/2001	Dennis A. Carson	220002062900	5759

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EXAMINER

YU, MISOOK

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/847,102

Applicant(s)

CARSON ET AL.

Examiner

MISOOK YU, Ph.D

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 March 2005.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8, 16, 28 and 29 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-8, 16, 28 and 29 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 03/22/05.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's submission filed on 03/22/2005 has been entered. Claim 1 has been amended. Claims 1-8, 16, 28, and 29 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The rejection of claims 1-8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of the amendment.

Claims 1-8, 16, 28, and 29 **remain rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn because applicant's argument is persuasive. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

This new matter rejection is made because of the limitation added in the amendment filed on 06/04/2005, i.e. "the antibody inhibits growth of the malignant cell that expresses the frizzled 5 receptor" in claims 1, and 16, the limitation "wherein the antibody is effective for immunotherapy of a malignant cell that overexpresses the frizzled 5 receptor" in claim 28.

The following is the summary of applicant's argument traversing the new matter rejection of record:

There is no in haec verba requirement for newly added claim limitations and those limitations can be supported by express, implicit, or inherent disclosure. MPEP 2163 IB.

The application discloses antibodies that bind to extracellular epitopes of frizzled proteins. Frizzled 5 is a member of the frizzled protein family disclosed throughout the specification, e.g., at page 8, lines 3-5 and at Table 1, page 9. At page 28, lines 9-12, the specification discloses that, although frizzled 2 is disclosed as an exemplary frizzled protein for the development of antibodies that inhibit malignant cell growth or that can be used as immunotherapies, other frizzled proteins, e.g., frizzled 5, can be used as antigens to develop antibodies for use in the disclosed methods.

With regard to the rejection of claims 1 and 16 for recitation of the phrase "the antibody inhibits growth of a malignant cell that expressed the frizzled 5 receptor," the specification at page 22, lines 14-16 discloses that the anti-frizzled antibodies affect cellular function by, e.g., cell growth inhibition. Thus, this cited claim amendment does not add new matter.

With regard to the rejection of claim 28 for recitation of the phrase "wherein the antibody is effective for immunotherapy of a malignant cell that overexpresses the frizzled 5 receptor," at page 21, line 24 through page 22, line 2 discloses use of antibodies that bind to the extracellular portion of a frizzled protein, e.g., frizzled 5 antibodies, and that kill or inhibit growth of tumor cells on binding, and so can be used

for immunotherapy. In addition, immunotherapy using anti-Fz antibodies is also described at page 26, lines 6-13. Thus, this cited claim amendment does not add new matter.

The Federal Circuit has ruled that "as long as an applicant has disclosed a 'fully characterized antigen's either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen." *Noelle v. Lederman*, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004). The structure of the Fzd 5 antigen is disclosed as SEQ ID N0:68 in the application.

These arguments have been fully considered but found unpersuasive. The Office agrees with applicant that there is no *in haec verba* requirement for a newly added limitation as long as the limitation is supported by express, implicit, or inherent disclosure in the specification as originally filed. However, the Office is unable to find express, implicit, or inherent support in the specification as originally disclosed for the rejected limitations. This new matter rejection is not about the specification does not have a support for Frizzled 5 being a member of the frizzled protein family.

The disclosure of the specification at page 28, 1st paragraph including lines 9-12 (applicant specifically points out where the support exists) is as follows:

As described above in Examples 1 to 4, frizzled 2 antigens may be differentially overexpressed in cells of malignant phenotype, whereas many frizzled gene products may be expressed in normal and abnormal cells. Whereas the frizzled 2 systems is exemplary herein, it is readily apparent that tumor specific frizzled antigens from the other frizzled genes are equally attractive targets for cancer immunotherapies. Accordingly, the methods taught herein can easily be adapted to other frizzled genes and their protein products.

The above disclosure reasonably communicates that there are many frizzled gene products, and frizzled gene products other than frizzled 2 could be a target for

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cancer therapy. However, there is no support either implicit or explicit for the limitation "the antibody inhibits growth of the malignant cell that expresses the frizzled 5 receptor". There is a support for genus, i.e. any member of frizzled gene products, but there is no support for the specifically claimed species, i.e. an antibody "inhibits growth of the malignant cell that expresses the frizzled 5 receptor", wherein the epitopes the antibody lies within the specific residues of the frizzled 5 protein.

As for disclosure of the specification at page 21, line 24 through page 22, line 2, page 22, lines 14-16 where applicant specifically points out the support for the limitations rejected for new matter could be found, the specification at page 22 lines 14-16 is about a mode of administration of a pharmaceutical, not about the rejected limitations. The Office assumes that lines 14-16 is a typographical error by applicant. The specification as originally filed at pages 21, and 22 under the heading "Immunotherapeutics" has following disclosure:

One aspect of the present invention is the design of immunotherapies for cancer. Wnt signaling through frizzled receptors has been described to inhibit apoptosis. Also, some of the genes that are regulated by TCF/beta-catenin are known to be associated with the cell cycle and cell proliferation. By blocking the binding of Wnt proteins to their receptors via antibodies directed to the extracellular portion of frizzled receptors, this pathway can be interrupted. Thus, it is believed that disruption of the downstream translocation of beta-catenin to the nucleus results in slower tumor growth or death of the cell.

As used herein, the term "modulating a biological activity of a malignant cell" refers to the ability of the antibody to effect cellular function. These effects may manifest themselves as cell growth inhibition, the ability to elicit a cytotoxic response to the malignant cell, or other such negative effects on the malignancy. Although not wishing to be bound to any particular theory, it is believed that this effect is caused by the antibody binding to the extracellular domain of the frizzled receptor in a way that interferes with the Wnt/frizzled signalling pathway.

This disclosure also reasonably communicates that there are many frizzled gene products, and frizzled gene products could be the target for cancer therapy because frizzled proteins work in the Wnt signaling system involved in cell cycle and cell

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proliferation. However, there is no support either implicit or explicit for the limitation "the antibody inhibits growth of the malignant cell that expresses the frizzled 5 receptor".

As for the argument with the disclosure at page 26, lines 6-13, applicant is arguing a limitation present in the claims. The following is the disclosure at page 26, i.e. Example 3, with the heading "The Effects of Anti-Fz Abs on Cancer Cell Growth":

The ability to block the Wnt-frizzled signaling pathway can provide an effective way of limiting growth of tumor cells. In order to determine the efficacy of using such anti-Fz Abs as an adjunctive passive immunotherapy, such as that observed using humanized anti-HER2 antibodies (Herceptin, Genentech, inc., South San Francisco, Calif.), the effects of anti-frizzled 2 antibodies on the growth of HNSCC cells was studied. Soluble inhibitors of frizzled receptors have been described to induce apoptosis secondary to their inhibition of frizzled signaling. Accordingly, this experiment was designed to test the efficacy of anti-Fz Abs to perform the same function.

Cell proliferation was determined by a colorimetric MTT-based assay. Briefly, either 7.5.times.10.sup.3 or 10.times.10.sup.3 SNU1076 cells per well were cultured in a 96 well plate. After 24 hour graded amounts of polyclonal goat anti-human frizzled-2 antibody containing 300 ng, 30 ng, 3 ng, and 0.3 ng were added in the culture medium. The same concentrations of goat serum or Goat antihuman IgG (Fisher Scientific, Pittsburgh, Pa.) were used as an isotype control. On 1, 2, 3, or 4 days after incubating antibody, 20 ul of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide)-based solution was added to the wells for four hours prior to lysis with 15% SDS, 0.015 M HCl. Absorbances at 570 and 650 nm were measured. The results are depicted in FIG. 4 and also given in Table IV below. Data represent the normalized growth fraction of the specific antibody treated cells to that of the control antibody treated cells (in triplicate).

This disclosure has support for frizzled 2, not frizzled 5 (SEQ ID NO:68).

As for the argument with the structure of the Fzd 5 antigen being disclosed as SEQ ID NO:68 in the application, applicant's argument is not commensurate in scope of the claims because the scope of the claims does not include any antibody that binds to the extracellular domain of the Fzd 5 antigen being disclosed as SEQ ID NO:68. During the prosecution history (note especially page 6, 1st paragraph of the reply filed on 06/04/2004), where applicant argued that "The claims are directed to antibodies that bind to the amino terminal extracellular domain of the frizzled 5 receptor, and that inhibits growth of a malignant cell that expresses the frizzled 5 protein. "

Claims 1-8, 16, 28, and 29 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **enablement requirement**. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are interpreted as drawn to an antibody binding to SEQ ID NO:68, or pharmaceutical comprising said antibody, wherein said antibody inhibits growth of a malignant cell that expresses the frizzled 5 receptor.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is ☐undue☐ include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicant argues that the disclosure adequately teaches how to make and use the claimed antibodies and how to identify malignant cells that over-express a frizzled 5 antigen. Even if the claimed frizzled 5 antibodies are not therapeutic for treatment of all cancers, claims reading on inoperative embodiments are enabled if the skilled artisan understand how to avoid inoperative embodiments. see, *In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971)). In the present application, one of skill would know how to avoid inoperative embodiments and identify the claimed antibodies without

undue experimentation. Moreover, the present application provides guidance in the form of assays and working examples for inhibition of malignant cell growth using anti-frizzled antibodies.

In response to the rejection due to the preamble recitation of "pharmaceutical" in claims 16, 28, and 29, applicant argues (note 1st paragraph of page 8 of the reply filed on 22 March 2005) that the enablement requirement can be met by using an in vitro or in vivo model that correlates with a given condition. Applicants have provided an in vitro system of testing administration of the claimed antibodies for inhibition of cancer cell growth or apoptosis of cancer cells at Examples 3 and 4, at pages 26-28. One of skill would recognize that this model correlates with the pharmaceutical uses of the claimed antibodies.

These arguments have been fully considered but found unpersuasive. The facts in *In re Cook and Merigold*, and those in the instant case are different in that the application of *In re Cook and Merigold* discloses six operative embodiments of the claimed invention. Note the top of page 301 of *In re Cook and Merigold*, 169 USPQ 299 under the heading "**Rejection**". In the instant case, the specification does not provide a single operative embodiment of the claimed invention, let alone six examples of the claimed invention as in the case of *In re Cook and Merigold*. The instant specification at Examples 3 and 4, at pages 26-28 does not disclose a single species of the claimed antibody. Rather, it is about anti-frizzled 2, and Her-2 that inhibits growth of malignant cells. Therefore arguing with an antibody disclosed at Examples 3 and 4, at pages 26-28 is considered as argument not commensurate in scope of claims. In summary, the

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instant specification has not demonstrated how to make a single species of the claimed genus if the claimed invention could ever be existed. In order to figure this out, one has to make an antibody against the extracellular domain of SEQ ID NO: 68, followed by screening those antibodies using the assay disclosed in Example 2 of the specification to see whether any one of the monoclonal antibodies would have the function recited in the claims. Applicant is reminded that the law requires that the disclosure of an application shall inform those skilled in the art how to make and/or obtain the alleged discovery for use, not how to screen it if it ever exists.

At the paragraph bridging pages 6, and 7 of the reply, applicant argues that the specification teaches that frizzled proteins are over-expressed in certain cancers and uses the frizzled 2 protein as an example for the frizzled protein family. See, e.g., specification, Examples 1 and 2, pages 23-26. The specification also discloses that the wnt/fzd pathway is implicated in tumorigenesis and that this signaling pathway converges on regulation of the beta-catenin protein, a transcription factor that is linked to carcinogenesis. See, e.g., specification at page 7, lines 16-26. The specification teaches that blockage of the wnt/fzd pathway signaling can limit tumor cell growth, that inhibition of frizzled signaling can induce apoptosis, and that anti-frizzled antibodies that block signaling can be used to limit tumor cell growth by immunotherapy. See, e.g., specification at page 21, line 24 through page 22, line 9, and page 26, line 6 through page 28, line 2. Again, the frizzled 2 protein is used as an example for the frizzled protein family and the specification teaches that for some cancers other frizzled

proteins, including frizzled 5, can be used. See, e.g., specification at page 28, lines 6-12.

These arguments have been fully considered but found unpersuasive because applicant arguments with frizzled 2 is considered as arguing with a limitation not present in the claims. The claimed invention is drawn to an antibody to frizzled 5, not frizzled 2. The Office is not disputing the scientific facts that frizzled receptors are involved in wnt/zd signaling. The claims are rejected because the specification fails to teach how to make and use the claimed antibody.

At 1st paragraph of page 7 of the reply, applicant argues the specification teaches how to make and use the claimed antibodies based on the current state of art making antibody. Antibody production is disclosed at page 18-20 of the specification. Exhibit A, a printout of an Antibody Resource website listing 89 suppliers of custom antibodies was supplied. The earliest priority application was filed on May 1, 2001. Thus, the technology of antibody production was well-known to and commercially available to those of skill in the art at the time of filing.

These arguments have been fully considered but found unpersuasive because applicant argument is not commensurate in scope of the claims. This enablement rejection is not about one of skill would not be able to make an antibody from a known protein sequence. During the prosecution history (note especially page 6, 1st paragraph of the reply filed on 06/04/2004) in response to the rejection of claims 1-8, 16, 22, 28, and 29 under 35 U.S.C. 103(a) as being unpatentable over any one of Tanaka et al (IDS, #1711998, Proc. Natl. Acad. Sci. USA. vol. 95, pages 10164-9), He et al (IDS #

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93, 1997, Science vol. 275, pages 1652-4), or Wang et al (IDS #184, 1996, J. Biol. Chem. vol. 271, pages 4468-76) in view of Campbell, A. (1986, Monoclonal antibody technology, chapter 1 only, Elsevier Science Publishers B.V., Netherlands) in the Office action mailed on 04 August 2003, applicant argued that the claimed invention is directed to antibodies that bind to the amino terminal extracellular domain of the frizzled 5 receptor, and that inhibits growth of a malignant cell that expresses the frizzled 5 protein. " The submitted Exhibit A does not demonstrate that any of the 88 custom antibodies making commercial vendors could make antibodies that bind to the amino terminal extracellular domain of the frizzled 5 receptor, **and** that inhibits growth of a malignant cell that expresses the frizzled 5 protein. If applicant states on the record that the claimed invention is drawn to antibodies made by any one of the 88 custom antibodies making commercial vendors using the protein sequence disclosed by any one of Tanaka et al (IDS, #1711998, Proc. Natl. Acad. Sci. USA. vol. 95, pages 10164-9), He et al (IDS # 93, 1997, Science vol. 275, pages 1652-4), or Wang et al (IDS #184, 1996, J. Biol. Chem. vol. 271, pages 4468-76), then the previously withdrawn rejection under 35 U.S.C. 103(a) as being unpatentable over any one of Tanaka et al (IDS, #1711998, Proc. Natl. Acad. Sci. USA. vol. 95, pages 10164-9), He et al (IDS # 93, 1997, Science vol. 275, pages 1652-4), or Wang et al (IDS #184, 1996, J. Biol. Chem. vol. 271, pages 4468-76) in view of Campbell, A. (1986, Monoclonal antibody technology, chapter 1 only, Elsevier Science Publishers B.V., Netherlands) for claims 1-8, 16, 28, and 29 would be instated.

Applicant argues beginning 2nd paragraph of page 7 of the reply the methods to detect over-expression of Frizzled 5 gene products using nucleic acid hybridization and amplification techniques, including specific primers, are disclosed at pages 18- 20 of the specification. Methods to detect over-expression of Frizzled 5 protein using specific antibodies are disclosed at pages 20-21 of the specification. The techniques above could be routinely carried out by laboratory technicians allowing routine screening of large numbers of cells if necessary. Moreover, panels of cancer cells and normal cells for expression screening were available to the user at the time of filing as disclosed at page 28, lines 13-20 of the specification. The disclosed panel of cancer cells includes, e.g., a renal cancer cell line. In addition, at the last paragraph of page 7 of the reply, applicant argues frizzled 5 is over-expressed in cancer cells as supported by Exhibit B, Janssens et al., Tumor Biology 25:161-171 (2004); which discloses that the frizzled 5 protein is over-expressed in renal cell carcinomas. At page 8, also argues that Zang et al., does not disclose the claimed antibodies directed against SEQ ID NO:68.

These arguments have been fully considered but found unpersuasive. As for applicant's argument that Zang et al., not disclosing the claimed antibodies, the rejection is about the specification failing to comply with the enablement requirement under 35 U.S.C. 112, first paragraph, not about the claims being anticipated by Zang et al.

As for arguments with Exhibit B, it is noted that Janssens et al., do not disclose any antibody binding to frizzled 5, wherein the antibody inhibits growth of the malignant cell that express the frizzled 5 receptor. What Janssens et al., teach is that FZD5 is

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over-expressed in renal cancer carcinoma tissue as shown at Table 2. The specification does not teach that FZD5 is over-expressed in renal cancer carcinoma tissue (obtained from cancer patients). The specification at page at page 28, lines 13-20 says that RpMI-8226 (in vitro renal cancer cell line cells) could be used to see whether other frizzled antigens other than the exemplary frizzled 2 are over-expressed. The specification does not teach what Janssens et al., teach.

As stated before in the previous Office action, the specification does not teach whether an anti-frizzled 5 antibody would inhibit growth of a malignant cell that expresses the frizzled 5 receptor. However, Rhee et al., (Sep. 26, 2002, *Oncogene* vol. 21, issue 43, pages 6598-605) teach at page 6599, left column, under the heading *Expression of Wnt and Fz mRNAs in HNSCC* that "When compared to the housekeeping gene G3PDH, all the Wnts, as well as Fz-2, were expressed more frequently in HNSCC than in normal cells, while there was no difference in Fz-5 gene expression". This suggests that the frizzled 5 receptor might not be expressed on a malignant cell. Note some of authors of the peer-reviewed journal article are the inventors of the instant application. It appears that Janssen et al., and Rhee et al., disclose conflicting data regarding frizzled 5 protein as cancer antigen. No where in the reply, applicant explains why the inventors of the instant application concluded that Frizzled 5 is not a cancer antigen. Based on the current state of art, in order to determine whether a human protein is a cancer antigen or not requires an undue experimentation. Based on confirmation of a cancer antigen as a first step, one of skill in the art would still be forced to screen whether an antibody against the cancer antigen

would inhibit growth of the cancer cell expressing the antigen in order to arrive at the instantly claimed invention. All these require an undue experimentation as demonstrated by Rhee et al., in view of Janssens et al. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for them.

Considering the unpredictable state of art, limited guidance, no examples in the specification how to use the instantly claimed invention, broad breadth of the claims, it is concluded that undue experimentation is required to practice the invention.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D whose telephone number is 571-

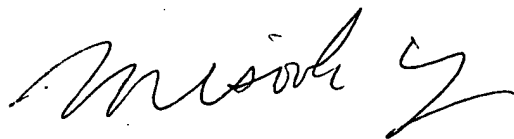
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272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D
Examiner
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A handwritten signature in black ink, appearing to read "Misook Yu", with a stylized flourish at the end.